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L1: Entry 1 of 4

File: USPT

Mar 19, 2002

DOCUMENT-IDENTIFIER: US 6358710 B1

TITLE: Humanized antibodies that bind to the antigen bound by antibody NR-LU-13

Detailed Description Paragraph Right (33):

Radioimmunoassay, immunoprecipitation and Fluorescence-Activated Cell Sorting (FACS) analysis have been used to determine reactivity profiles of NR-LU-10. The NR-LU-10 target antigen is present on either fixed cultured cells or in detergent extracts of various types of cancer cells. For example, the NR-LU-10 antigen is expressed by small cell lung, non-small cell lung, colon, breast, renal, ovarian, pancreatic, and other carcinoma tissues. Tumor reactivity of the NR-LU-10 antibody is set forth in Table A, while NR-LU-10 reactivity with normal tissues is set forth in Table B. The values in Table B are obtained as described below. Positive NR-LU-10 tissue reactivity indicates NR-LU-10 antigen expression by such tissues. The NR-LU-10 antigen has been further described by Varki et al., "Antigens Associated with a Human Lung Adenocarcinoma Defined by Monoclonal Antibodies," Cancer Research 44: 681-687 (1984), and Okabe et al., "Monoclonal Antibodies to Surface Antigens of Small Cell Carcinoma of the Lung," Cancer Research 44: 5273-5278 (1984).

Detailed Description Paragraph Right (114):

One skilled in the art, based on the teachings in this application and the applications referenced herein, can readily determine an effective diagnostic or therapeutic effective dosage and treatment protocol. This will depend upon factors such as the particular selected therapeutic or diagnostic agent, route of delivery, the type of target site(s), affinity of the targeting moiety for target site of interest, any cross-reactivity of the targeting moiety with normal tissue, condition of the patient, whether the treatment is effected alone or in combination with other treatments, among other factors. A therapeutic effective dosage is one that treats a patient by extending the survival time of the patient. Preferably, the therapy further treats the patient by arresting the tumor growth and most preferably, the therapy further eradicates the tumor.

Other Reference Publication (34):

Herlyn et al., "CO 17-1A and Related Monoclonal Antibodies: Their Production and Characterization," Hybridoma 5(Suppl. 1): S3-S10, 1986.

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TUMOUR.USPT.	4334
TUMOR.USPT.	36691
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TUMOURS.USPT.	2581
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<u>L3</u>	L2 and normal	37	<u>L3</u>
<u>L2</u>	'KS1/4'	48	<u>L2</u>
<u>L1</u>	('CO 17-1A') and normal	4	<u>L1</u>

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(L3 AND (TAA OR TUMOR OR TUMOUR)).USPT.	37

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<u>L4</u>	L3 and (TAA or tumor or tumour)	37	<u>L4</u>
<u>L3</u>	L2 and normal	37	<u>L3</u>
<u>L2</u>	'KS1/4'	48	<u>L2</u>
<u>L1</u>	('CO 17-1A') and normal	4	<u>L1</u>

END OF SEARCH HISTORY

AUTHOR ADDRESS: (a)Nucl. Med., MS 309, Hahnemann Univ., Broad and Vine  
Sts., Philadelphia, PA 19102-1192\*\*USA  
JOURNAL: Cancer (Philadelphia) 73 (3 SUPPL.):p884-889 1994  
ISSN: 0008-543X  
DOCUMENT TYPE: Article  
RECORD TYPE: Abstract  
LANGUAGE: English

ABSTRACT: Background. The monoclonal antibody anti-epidermal growth factor receptor (EGFr)antibody-425, against the epidermal growth factor receptor, has the potential to bind specifically to gliomas and not **normal** brain tissue. A prospective study was conducted (1986-1988) to evaluate the use of Indium-111 (111In)-labeled anti-EGFr-425 in the localization of gliomas before radioimmunotherapy with Iodine-125 (125I)-labeled anti-EGFr-425. Methods. Twenty-eight patients with intracranial neoplasms were injected intravenously with an average dose of 2.2 mCi 111In-labeled anti-EGFr-425. Planar and single-photon emission computed tomography scans were performed after 48 and 72 hours. Control studies also were performed in two cases with 111In-labeled Co 17-1A (an antibody to colorectal cancer) and in one case with unlabeled 111In chloride. Results. The immunoscintigraphic findings were generally in good agreement with computerized tomographic findings. The definitive diagnosis was established by biopsy findings: 23 gliomas (1 Grade I, 5 Grade II, 6 Grade III, and 11 Grade IV), 1 meningioma, and 4 metastatic lesions. The localization of gliomas with 111In-labeled anti-EGF-425 had a sensitivity of 0.96, a specificity of 0.60 and an accuracy of 0.90. Conclusion. Immunoscintigraphy with 111In labeled anti-EGFr-425 can be useful in the management of malignant gliomas, especially before radioimmunotherapy with 125I-labeled anti-EGFr-425.

2/7/3 (Item 1 from file: 73)  
DIALOG(R)File 73:EMBASE  
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03480726 EMBASE No: 1987233307  
Rapid dissociation of adherent human tumor cells by ultrasound  
Menssen H.D.; Herlyn M.; Rodeck U.; Koprowski H.  
The Wistar Institute of Anatomy and Biology, Philadelphia, PA 19104  
United States  
Journal of Immunological Methods ( J. IMMUNOL. METHODS ) (Netherlands)  
1987, 104/1-2 (1-6)  
CODEN: JIMMB ISSN: 0022-1759  
DOCUMENT TYPE: Journal  
LANGUAGE: ENGLISH

Cultured human melanoma and gastrointestinal carcinoma cells were detached from substrate and further dissociated by placing the culture vessel into a water-filled ultrasonic cleaner (43 kHz) and sonicating it for 10-50 s. Plating efficiency and long-term growth of three melanoma cell lines were similar after ultrasound or trypsin detachment. Binding of monoclonal antibodies that define **normal** and tumor-associated antigens on melanoma and colorectal carcinoma cells was not affected by ultrasound in 21 out of 23 cases. The 40 kDa colorectal carcinoma-associated antigen defined by monoclonal antibody CO 17-1A was more highly expressed after ultrasonication than trypsinization. The antigen defined by antibody CO 44.1 on these cells was more sensitive to sonication. This method represents a rapid, effective and gentle alternative to trypsin detachment of cultured cells, especially when repeated cell washing or centrifugation steps are required.

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s (CO(W)17(w)1A) and expression  
1960348 CO  
964790 17  
57617 1A  
24 CO(W)17(W)1A  
1884546 EXPRESSION  
S3 11 (CO(W)17(W)1A) AND EXPRESSION

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S4 5 RD S3 (unique items)

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4/7/1 (Item 1 from file: 5)  
DIALOG(R)File 5:Biosis Previews(R)  
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12984209 BIOSIS NO.: 200100191358

Immunogenicity of recombinant GA733-2E antigen (CO17-1A, EGP, KS1-4, KSA, Ep-CAM) in gastro-intestinal carcinoma patients.

AUTHOR: Staib Ludger; Birebent Brigitte; Somasundaram Rajasekharan; Purev Enkhtsetseg; Braumueller Heidi; Leeser Christian; Kuettner Norbert; Li Weiping; Zhu Dawei; Diao Jun; Wunner William; Speicher David; Beger Hans-Guenther; Song Hong; Herlyn Dorothee(a)

AUTHOR ADDRESS: (a)Wistar Institute, 3601 Spruce Street, Philadelphia, PA, 19104: Dherlyn@wistar.upenn.edu\*\*USA

JOURNAL: International Journal of Cancer 92 (1):p79-87 1 April, 2001

MEDIUM: print

ISSN: 0020-7136

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

SUMMARY LANGUAGE: English

ABSTRACT: Targeting the GA733 antigen (also known as CO17-1A, EGP, KS1-4, KSA, Ep-CAM) by monoclonal antibody CO17-1A or anti-idiotypic antibodies mimicking the CO17-1A or GA733 epitope has induced prolonged survival and specific immune responses to the antigen, respectively, in colorectal cancer (CRC) patients. In pre-clinical studies in mice and rabbits, recombinant baculovirus-derived GA733-2E antigen was superior to anti-idiotypic antibodies at modulating specific immune responses. Our aim was to evaluate the immunogenicity and potential toxicity of alum-precipitated GA733-2E in a phase I trial in patients with resected CRC or pancreatic cancer. Six patients with advanced pancreatic carcinoma and 6 with CRC Dukes' stage A, B or C received between 4 and 7 doses of alum-precipitated GA733-2E at 50, 200 or 800 mug/dose at monthly intervals. Antibody binding to GA733-2E or antigen-positive CRC cells was determined, as were antigen-specific proliferative, cytolytic T-lymphocyte and delayed-type hypersensitivity responses. Six of the 12 patients developed antigen-specific humoral immune responses after immunotherapy, and 8 developed cellular immune responses. The overall immune response rate, including patients with humoral and/or cellular immune responses, was 83%. Median overall survival of the CRC and pancreatic cancer patients was 39.8 and 11.2 months, respectively. Following 18 years of single-epitope targeting of the GA733 antigen, immunization of patients against multiple epitopes of the antigen frequently induces an immune response in the absence of significant toxicity, despite relatively widespread **expression** of this antigen on normal epithelial cells.

4/7/2 (Item 2 from file: 5)  
DIALOG(R)File 5:Biosis Previews(R)  
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08751628 BIOSIS NO.: 199395040979

Lack of effect of recombinant human interferon-alpha-2b on **expression** of 17-1A antigen on human colon cancer cells.

AUTHOR: Oredipe Oladipo A; Barth Rolf F(a); Rotaru Joan H; Steplewski Zenon

AUTHOR ADDRESS: (a)Ohio State Univ., Dep. Pathol., 165 Hamilton Hall, 1645 Neil Ave., Columbus, Ohio 43210

JOURNAL: Hybridoma 11 (5):p607-615 1992

ISSN: 0272-457X

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: The effects of recombinant human interferon alpha (rHuIFN-alpha-2b) on cell growth, **expression** of antigenic receptor sites (r) and the affinity constant (K-a) of monoclonal antibody CO 17-1A IgG were studied on two human colorectal cancer cell lines, CX-1 and SW 1116. Cells were incubated with varying concentrations of rHuIFN-alpha-2b prior to exposure to 125I-labeled 17-1A IgG at 37 degree C following which r and K-a were determined by means of Scatchard plots. Varying concentrations of rHuIFN-alpha-2b had significant growth inhibitory effects on CX-1 and SW 1116 cells, which were time and concentration dependent, but no effects on **expression** of r and K-a compared to controls. Our data indicate that rHuIFN-alpha-2b does not invariably increase the **expression** of tumor-associated antigens and that this effect may be independent of its antiproliferative activity. The in vitro response or lack thereof of neoplastic cells to rHuIFN-alpha-2b may be useful to identify those patients who potentially might gain from a clinical course of rHuIFN-alpha-2b for either therapeutic or diagnostic purposes.

4/7/3 (Item 3 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

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07342859 BIOSIS NO.: 000090122761

ALTERATIONS IN MONOCLONAL ANTIBODY AFFINITY AND ANTIGENIC RECEPTOR SITE **EXPRESSION** ON MYCOPLASMA-INFECTED HUMAN COLORECTAL CANCER CELLS

AUTHOR: OREDIPE O A; BARTH R F; ROTARU J H; HINKLE G H; STEPLEWSKI Z

AUTHOR ADDRESS: OHIO STATE UNIV., DEP. PATHOL., 4170 GRAVES HALL, 333 WEST 10TH AVE., COLUMBUS, OHIO 43210.

JOURNAL: PROC SOC EXP BIOL MED 194 (4). 1990. 301-307. 1990

FULL JOURNAL NAME: Proceedings of the Society for Experimental Biology and Medicine

CODEN: PSEBA

RECORD TYPE: Abstract

LANGUAGE: ENGLISH

ABSTRACT: The affinity of MoAb CO 17-1A and **expression** of its antigenic target were studied on uninfected and mycoplasma-infected colorectal cancer cell lines SW 1116 and SW 948. Binding of 125I-labeled CO 17-1A to SW 1116 cells was quantified at 37.degree. C by determination of the affinity constant (Ka) and the number of antigenic receptor sites (r) per cell using Scatchard plots. When mycoplasma-free SW 1116 cells were used as targets, Ka was 0.92 +/- 0.06 .times. 108 M-1 and r = 1.32 +/- 0.14 .times. 106 at 37.degree. C. One batch of unspiciated, mycoplasma-infected SW 1116 cells had reduced affinity and a decreased number of antigenic receptor sites per cell for 125I-labeled 17-1A, while another batch of infected SW 1116 cells had a 4- to 5-fold increase in r and diminished Ka for the antibody compared with uninfected cells. When unspiciated, mycoplasma-infected SW 948 cells were exposed to 125I-labeled 17-1A and the data subjected to Scatchard analysis, the affinity of the antibody deviated markedly from linearity and rendered analysis for Ka and r meaningless. These data



indicate that mycoplasma infection can produce variable effects on the cellular **expression** of antigenic receptor sites and the affinity of antibody for its target, and emphasize the importance of using mycoplasma-free cell lines in studies of these parameters.

4/7/4 (Item 1 from file: 73)  
DIALOG(R)File 73:EMBASE  
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07561732 EMBASE No: 1999045554  
Tumor-antigen heterogeneity of disseminated breast cancer cells:  
Implications for immunotherapy of minimal residual disease  
Braun S.; Hepp F.; Sommer H.L.; Pantel K.  
S. Braun, I. Frauenklinik, Klinikum Innenstadt,  
Ludwig-Maximilians-Universitat, Maistrasse 11, D-80337 Munich Germany  
AUTHOR EMAIL: sbraun@fk-i.med.uni-muenchen.de  
International Journal of Cancer ( INT. J. CANCER ) (United States) 1999  
, 84/1 (1-5)  
CODEN: IJCNA ISSN: 0020-7136  
DOCUMENT TYPE: Journal; Article  
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH  
NUMBER OF REFERENCES: 30

Single micrometastatic tumor cells encased in mesenchymal tissues, such as bone marrow (BM), are regarded as suitable targets for adjuvant immunotherapy since they are easily accessible for both immunoglobulins and immune effector cells. However, the antigen profile of such cells, to which antibody therapy might be targeted, cannot be deduced from the antigen pattern of the primary tumor. To evaluate the antigen profile of disseminated cells found in BM aspirates from 20 breast cancer patients, we applied a quantitative immuno-cytochemical double-marker assay and typed for 4 common tumor-associated cell-surface antigens (cerbB-2, CO 17-1A, MUC-1, Lewis(Y)). Individual breast cancer cells were identified by F(ab) fragments of the pan- cytokeratin (CK) monoclonal antibody (MAb) A45-B/B3, directly conjugated with alkaline phosphatase, which identified cancer cells as sensitively as the standard APAAP procedure ( $r = 0.998$ ;  $p < 0.0001$ ). CKsup + cells co-expressed c- erbB-2, CO17-1A, MUC-I and Lewis(Y) in 87%, 78%, 79% and 79% of patients, respectively; however, the frequency of double-positive cells per sample varied considerably. The mean percentage of double-positive cells per total number of CKsup + cells was 41% for c-erbB-2 (range 0-92%), 47% for CO 17-1A (range 0-75%), 49% for MUC-I (range 0-67%) and 32% for Lewis(Y) (range 0- 59%). In 14 of these patients, we used an antibody cocktail to type CKsup + cells for the combined **expression** of all 4 antigens. The antibody cocktail labeled significantly more CKsup + cells than each of the single MAbs alone, resulting in a mean of 71% double-positive tumor cells (34-100%). We conclude that **expression** of tumor-associated cell-surface antigens on micrometastatic cancer cells in BM is heterogeneous, which may limit the efficacy of monovalent immunotherapeutic strategies directed against only one particular antigen. Thus, defining target antigens expressed by the actual target cells emerges as a crucial first step in selecting appropriate therapeutic targets.

4/7/5 (Item 2 from file: 73)  
DIALOG(R)File 73:EMBASE  
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04622253 EMBASE No: 1991116296  
Human anti-murine immunoglobulin responses and immune functions in cancer patients receiving murine monoclonal antibody therapy  
Blottiere H.M.; Steplewski Z.; Herlyn D.; Douillard J.-Y.  
INSERM U211, Faculte de Medecine, 1 Rue Gaston Veil, 44035 Nantes Cedex

France

Human Antibodies and Hybridomas ( HUM. ANTIBODIES HYBRIDOMAS ) (United States) 1991, 2/1 (16-25)

CODEN: HANHE ISSN: 0956-960X

DOCUMENT TYPE: Journal; Article

LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

In our institution, over 200 patients with gastro-intestinal tract carcinomas have been treated with monoclonal antibodies (MAbs) including CO 17-1A. In one clinical trial, MAbs were administered in combination with gamma interferon. Natural killer cell cytotoxicity (NK) and antibody-dependent cell-mediated cytotoxicity (ADC) were studied in patients before treatment. Very low NK and ADCC activities were measured in metastatic cancer patients. NK cell lysis was enhanced during gamma-interferon treatment, associated with a modification of the Fc receptor **expression**, but no changes in the ADCC reactivities of leukocytes were noticed. Monoclonal antibodies were circulating for one to four weeks after a single dose infusion, independent of the patients' immune responses toward the administered MAb. Sixty-three percent of the patients mounted an anti-mouse immunoglobulin response. Anti-idiotypic antibodies were detected in 70% of the responding patients. Variations in the anti-mouse Ig responses were dependent on the therapeutic protocol. The immune responses were composed of IgM, IgA, and IgG (mainly IgG1, often associated with IgG2 and/or IgG3). In patients receiving MAbs together with gamma-interferon, development of the anti-mouse Ig responses were delayed with an increase in the anti-isotypic component and a decrease in the anti-idiotypic component as compared to patients treated with MAb alone. No correlation could be established with clinical results.

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 DIALOG(R)File 5:Biosis Previews(R)  
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12984209 BIOSIS NO.: 200100191358  
 Immunogenicity of recombinant GA733-2E antigen (CO17-1A, EGP, KS1-4, KSA, Ep-CAM) in gastro-intestinal carcinoma patients.  
 AUTHOR: Staib Ludger; Birebent Brigitte; Somasundaram Rajasekharan; Purev Enkhtsetseg; Braumueller Heidi; Leeser Christian; Kuettner Norbert; Li Weiping; Zhu Dawei; Diao Jun; Wunner William; Speicher David; Beger Hans-Guenther; Song Hong; Herlyn Dorothee(a)  
 AUTHOR ADDRESS: (a)Wistar Institute, 3601 Spruce Street, Philadelphia, PA, 19104: Dherlyn@wistar.upenn.edu\*\*USA  
 JOURNAL: International Journal of Cancer 92 (1):p79-87 1 April, 2001  
 MEDIUM: print  
 ISSN: 0020-7136  
 DOCUMENT TYPE: Article  
 RECORD TYPE: Abstract  
 LANGUAGE: English  
 SUMMARY LANGUAGE: English

ABSTRACT: Targeting the GA733 antigen (also known as CO17-1A, EGP, KS1-4, KSA, Ep-CAM) by monoclonal antibody CO17-1A or anti-idiotypic antibodies mimicking the CO17-1A or GA733 epitope has induced prolonged survival and specific immune responses to the antigen, respectively, in colorectal **cancer** (CRC) patients. In pre-clinical studies in mice and rabbits, recombinant baculovirus-derived GA733-2E antigen was superior to anti-idiotypic antibodies at modulating specific immune responses. Our aim was to evaluate the immunogenicity and potential toxicity of alum-precipitated GA733-2E in a phase I trial in patients with resected CRC or pancreatic **cancer**. Six patients with advanced pancreatic carcinoma and 6 with CRC Dukes' stage A, B or C received between 4 and 7 doses of alum-precipitated GA733-2E at 50, 200 or 800 mug/dose at monthly intervals. Antibody binding to GA733-2E or antigen-positive CRC cells was determined, as were antigen-specific proliferative, cytolytic T-lymphocyte and delayed-type hypersensitivity responses. Six of the 12 patients developed antigen-specific humoral immune responses after immunotherapy, and 8 developed cellular immune responses. The overall immune response rate, including patients with humoral and/or cellular immune responses, was 83%. Median overall survival of the CRC and pancreatic **cancer** patients was 39.8 and 11.2 months, respectively. Following 18 years of single-epitope targeting of the GA733 antigen, immunization of patients against multiple epitopes of the antigen frequently induces an immune response in the absence of significant toxicity, despite relatively widespread expression of this

antigen on **normal** epithelial cells.

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12604874 BIOSIS NO.: 200000358376

**Cancer vaccines: Single-epitope anti-idiotypic vaccine versus multiple-epitope antigen vaccine.**

AUTHOR: Maruyama Haruhiko; Zaloudik Jan; Li Weiping; Sperlagh Melinda; Koido Takashi; Somasundaram Rajasekharan; Scheck Stacey; Prewett Marie; Herlyn Dorothee(a)

AUTHOR ADDRESS: (a)Wistar Institute of Anatomy and Biology, 36th Street at Spruce, Philadelphia, PA, 19104\*\*USA

JOURNAL: Cancer Immunology Immunotherapy 49 (3):p123-132 June, 2000

MEDIUM: print

ISSN: 0340-7004

DOCUMENT TYPE: Literature Review

RECORD TYPE: Abstract

LANGUAGE: English

SUMMARY LANGUAGE: English

**ABSTRACT:** In this study, we compared the immunogenicity and **tumor**-protective activity of anti-idiotypic antibodies mimicking a single **tumor**-associated epitope and **tumor**-associated antigen expressing multiple potentially immunogenic epitopes. We focused our study on the colorectal-carcinoma(CRC)-associated antigen GA733 (also known as CO17-1A/**KS1-4**/KSA/EpCAM). Monoclonal anti-idiotypic antibody (Ab2) BR3E4 was produced against murine anti-CRC mAb CO17-1A (Ab1) in rats. Full-length native GA733 protein was isolated from human **tumor** cells, and the extracellular domain protein (GA733-2E) was isolated from supernatants of recombinant baculovirus-infected insect cells by immunoaffinity chromatography. The immunomodulatory activity of the Ab2 was compared with that of the antigen, both in rabbits and in mice. Mice, like humans but not rabbits, express a GA733 antigen homologue on some of their **normal** tissues. Thus, these in vivo models allow the comparison of the immunogenicity of Ab2 and antigen in the presence (mice) and absence (rabbits) of **normal** tissue expression and immunological tolerance of the GA733 antigen homologue. In rabbits, aluminum-hydroxide(alum)-precipitated native GA733 antigen was superior to alum-precipitated Ab2 in inducing specific humoral immunity. In mice, alum-precipitated recombinant GA733-2E antigen, but not alum-precipitated Ab2, induced specific humoral immunity. However, when the Ab2 was administered to mice in Freund's complete adjuvant, specific humoral immune responses were elicited. Ab2 in complete Freund's adjuvant and GA733-2E in alum were compared for their capacity to induce antigen-specific cellular immunity in mice. Whereas lymphoproliferative responses were obtained with the recombinant antigen only, delayed-type hypersensitivity responses were obtained with both recombinant antigen and Ab2, although these responses were lower than after antigen immunization. The recombinant antigen in alum did not protect mice against challenge with antigen-positive syngeneic murine CRC cells. Similar studies with Ab2 BR3E4 mimicking the CO17-1A epitope were not possible because the **tumor** cells do not express this epitope after transfection with the human GA733-2 cDNA. However, similar studies with Ab2 mimicking the epitope defined by mAb GA733, which is expressed by the transfected **tumor** cells, indicated a lack of **tumor**-protective activity of this Ab2. In contrast, the full-length antigen expressed by recombinant adenovirus inhibited the growth of established tumors in mice. In conclusion, soluble antigen is a more potent modulator of humoral and cellular immune responses than Ab2, both administered in adjuvant. However, for induction of protective immunity, the immunogenicity of the antigen must be further enhanced, e.g., by

expression of the antigen in a viral vector.

8/7/3 (Item 3 from file: 5)  
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09553566 BIOSIS NO.: 199598008484  
Monoclonal antibody **KS1/4**-methotrexate immunoconjugate studies  
in non-small cell lung carcinoma.  
AUTHOR: Elias Darlene J(a); Kline Lawrence E; Robbins Bruce A; Johnson  
Henry C L Jr; Pekny Katherine; Benz Mitzi; Robb James A; Walker Leslie E;  
Kosty Michael; Dillman Robert O  
AUTHOR ADDRESS: (a)Div. Chest Critical Care Med., Scripps Clinic Res.  
Foundation, 10666 North Torrey Pines Road, La \*\*USA  
JOURNAL: American Journal of Respiratory and Critical Care Medicine 150 (4)  
):p1114-1122 1994  
ISSN: 1073-449X  
DOCUMENT TYPE: Article  
RECORD TYPE: Abstract  
LANGUAGE: English

ABSTRACT: The antigen reactive with murine monoclonal antibody (MAb)  
**KS1/4** is expressed on epithelial malignancies and some  
normal epithelial tissues. Studies were undertaken to evaluate  
**KS1/4**-methotrexate (**KS1/4**-MTX) immunoconjugate in  
patients with advanced non-small cell carcinoma of the lung. Eleven  
patients in two different groups received **KS1/4**-MTX in two  
different escalating dose infusion schedules with a maximal tolerated  
dose of 1,750 mg/M-2 and a cumulative dose of MTX of 40 mg/M-2.  
Toxicities were similar in both groups and included fever, anorexia,  
nausea, vomiting, diarrhea, abdominal pain, guaiac positive stool, and  
hypoalbuminemia. Two patients had an associated aseptic meningitis. One  
patient had a 50% decrease in two lung nodules without a change in  
lymphangitic infiltrates. This patient received a second course of  
treatment and developed an immune complex-mediated arthritis and serum  
sickness. Four patients mounted a human antimouse antibody response.  
Post-treatment tumor biopsies documented binding of MAb **KS1/**  
**4**. These studies document the feasibility and potential usefulness  
of a MAb directed against tumor-associated antigens with the  
targeting of chemotherapeutic drugs in patients with non-small cell lung  
carcinoma.

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06619223 BIOSIS NO.: 000087061385  
MOLECULAR CLONING AND CHARACTERIZATION OF A HUMAN ADENOCARCINOMA-EPITHELIAL  
CELL SURFACE ANTIGEN COMPLEMENTARY DNA  
AUTHOR: STRNAD J; HAMILTON A E; BEAVERS L S; GAMBOA G C; APELGREN L D;  
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46285.  
JOURNAL: CANCER RES 49 (2). 1989. 314-317. 1989  
FULL JOURNAL NAME: Cancer Research  
CODEN: CNREA  
RECORD TYPE: Abstract  
LANGUAGE: ENGLISH

ABSTRACT: A human adenocarcinoma-associated antigen (KSA) defined by the  
monoclonal antibody **KS1/4** has become the focus of several  
site-directed strategies for tumor therapy. KSA, a 40,000 Da cell

surface glycoprotein antigen, is found at a high density in all adenocarcinomas examined to date and in corresponding **normal** epithelial tissues. Here we describe the cloning and sequencing of overlapping complementary DNA clones which encode the entire KSA as expressed in UCLA-P3, a human lung adenocarcinoma cell line. We have deduced the 314-amino acid sequence and have compared it to the N-terminal amino acid sequence data of the affinity-purified antigen. The KSA is synthesized as a 314-residue-long preproprotein that is then processed to a 232-residue-long antigen. KSA appears to have a single transmembrane domain of 23 residues that separates the highly charged 26-residue cytoplasmic domain from the extracellular domain. The N-terminal region of the propeptide is rich in cysteines and contains three potential N-glycosylation sites. Computer-assisted analyses at both the DNA and protein levels have found no significant similarities of this protein to known sequences, but a GC-rich 5' terminus is evident. Northern blot analysis shows that transcription of KSA can be detected in RNA isolated from **normal** colon but not in RNA isolated from **normal** lung, prostate, or liver.

8/7/5 (Item 5 from file: 5)  
DIALOG(R)File 5:Biosis Previews(R)  
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06270434 BIOSIS NO.: 000086104617  
CHARACTERIZATION OF THE HUMAN **TUMOR** AND **NORMAL** TISSUE  
REACTIVITY OF THE **KS1-4** MONOCLONAL ANTIBODY  
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JOURNAL: HYBRIDOMA 7 (4). 1988. 407-415. 1988  
FULL JOURNAL NAME: Hybridoma  
CODEN: HYBRD  
RECORD TYPE: Abstract  
LANGUAGE: ENGLISH

ABSTRACT: The tissue and **tumor** distribution of the antigen recognized by monoclonal antibody **KS1/4** was determined by a combination of immunoperoxidase techniques, flow cytometric analyses and solid phase enzyme-linked immunoassays. These data document that the **KS1/4** antigen is expressed in many epithelial malignancies and **normal** epithelial surfaces suggesting that this antigen represents an epithelial/epithelial malignancy marker.

8/7/6 (Item 6 from file: 5)  
DIALOG(R)File 5:Biosis Previews(R)  
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04267007 BIOSIS NO.: 000077093053  
ANTIGENS ASSOCIATED WITH A HUMAN LUNG ADENO CARCINOMA DEFINED BY MONO  
CLONAL ANTIBODIES  
AUTHOR: VARKI N M; REISFELD R A; WALKER L E  
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JOURNAL: CANCER RES 44 (2). 1984. 681-687. 1984  
FULL JOURNAL NAME: Cancer Research  
CODEN: CNREA  
RECORD TYPE: Abstract  
LANGUAGE: ENGLISH

ABSTRACT: Monoclonal antibodies **KS1/4** and **KS1/17** seemed to recognize similar glycoprotein antigens on the lung carcinoma cells by indirect immunoprecipitation and sodium dodecyl sulfate-polyacrylamide

gel electrophoresis analysis. However, mapping of [3H]lysine- and [3H]arginine-labeled tryptic peptides of antigens in specific immunoprecipitates of lung carcinoma cells by high-pressure liquid chromatography revealed a one peptide difference. Antibody KS1/9 did not immunoprecipitate any identifiable protein from detergent extracts of the immunizing cell line by routine methods and appears to detect a glycolipid antigen. Immunocytochemical analysis of tissue sections showed this monoclonal antibody to be reactive with adenocarcinomas of the lung and not with the other histological types of lung carcinoma or **normal** tissue. Monoclonal antibodies KS1/4 and KS1/17, however, reacted with 3 major histological types of lung **cancer** and minimally with the proximal tubules of **normal** kidney and the epithelium of bronchioles.

8/7/7 (Item 1 from file: 73)  
DIALOG(R) File 73:EMBASE  
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11639240 EMBASE No: 2002211310  
Monoclonal antibody 9C4 recognizes epithelial cellular adhesion molecule, a cell surface antigen expressed in early steps of erythropoiesis  
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Experimental Hematology ( EXP. HEMATOL. ) (United States) 2002, 30/6  
(537-545)  
CODEN: EXHEB ISSN: 0301-472X  
PUBLISHER ITEM IDENTIFIER: S0301472X02007981  
DOCUMENT TYPE: Journal ; Article  
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH  
NUMBER OF REFERENCES: 32

Objectives. Monoclonal antibody (mAb) 9C4 detects a surface antigen expressed on immature erythroid progenitor cells and epithelial **tumor** cell lines. The aim of this study was to identify the recognized surface antigen and to analyze a potential role of this molecule in early steps of erythropoiesis. Materials and Methods. A pituitary-derived retroviral cDNA library was used to generate viruses and infect NIH-3T3 fibroblasts. The transfected cells were stained with mAb 9C4; positive cells were sorted by FACS; and a clonal cell line binding mAb 9C4 was established. cDNA encoding the 9C4-binding protein was amplified by polymerase chain reaction and cloned. Reactivity of mAb 9C4 with human bone marrow (BM) cells was analyzed by flow cytometry. Results. Sequence analysis of the isolated cDNA uncovered a 100% identity with the epithelial cellular adhesion molecule (Ep-CAM). Two-color flow cytometric analysis revealed that almost 100% of Ep-CAMSUP+ BM cells coexpressed CD105, E-cadherin, and high levels of CD71. Fractions of Ep-CAMSUP+ BM cells also were CD34SUP+ but lacked glycophorin A expression, suggesting that Ep-CAMSUP+ cells represent immature erythroid cells. Reverse transcriptase polymerase chain reaction analysis of BM mononuclear cells revealed that the 9C4SUP+ erythroblast population but not the 9C4SUP- fraction expressed Ep-CAM mRNA. Peripheral blood CD34SUP+ cells induced in vitro to differentiate into the erythroid lineage showed strong Ep-CAM expression on days 3 to 7 of culture. The addition of Ep-CAM-specific mAbs 9C4 or KS1/4 to the culture resulted in two- to three-fold up-regulation of Ep-CAM protein expression. Conclusion. mAb 9C4 recognizes Ep-CAM, a molecule expressed in the early steps of erythropoiesis. (c) 2002 International Society for Experimental Hematology. Published by Elsevier Science Inc.

8/7/8 (Item 2 from file: 73)  
DIALOG(R) File 73:EMBASE

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07253961 EMBASE No: 1998110249

KSA antigen Ep-CAM mediates cell-cell adhesion of pancreatic epithelial cells: Morphoregulatory roles in pancreatic islet development

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Journal of Cell Biology ( J. CELL BIOL. ) (United States) 23 MAR 1998,  
140/6 (1519-1534)

CODEN: JCLBA ISSN: 0021-9525

DOCUMENT TYPE: Journal; Article

LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

NUMBER OF REFERENCES: 96

Cell adhesion molecules (CAMs) are important mediators of cell-cell interactions and regulate cell fate determination by influencing growth, differentiation, and organization within tissues. The human pancreatic carcinoma antigen KSA is a glycoprotein of 40 kD originally identified as a marker of rapidly proliferating tumors of epithelial origin. Interestingly, most normal epithelia also express this antigen, although at lower levels, suggesting that a dynamic regulation of KSA may occur during cell growth and differentiation. Recently, evidence has been provided that this glycoprotein may function as an epithelial cell adhesion molecule (Ep-CAM). Here, we report that Ep-CAM exhibits the features of a morphoregulatory molecule involved in the development of human pancreatic islets. We demonstrate that Ep-CAM expression is targeted to the lateral domain of epithelial cells of the human fetal pancreas, and that it mediates calcium-independent cell-cell adhesion. Quantitative confocal immunofluorescence in fetal pancreata identified the highest levels of Ep-CAM expression in developing islet-like cell clusters budding from the ductal epithelium, a cell compartment thought to comprise endocrine progenitors. A surprisingly reversed pattern was observed in the human adult pancreas, displaying low levels of Ep-CAM in islet cells and high levels in ducts. We further demonstrate that culture conditions promoting epithelial cell growth induce upregulation of Ep-CAM, whereas endocrine differentiation of fetal pancreatic epithelial cells, transplanted in nude mice, is associated with a downregulation of Ep-CAM expression. In addition, a blockade of Ep-CAM function by KS1/4 mAb induced insulin and glucagon gene transcription and translation in fetal pancreatic cell clusters. These results indicate that developmentally regulated expression and function of Ep-CAM play a morphoregulatory role in pancreatic islet ontogeny.

8/7/9 (Item 3 from file: 73)

DIALOG(R) File 73:EMBASE

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04901446 EMBASE No: 1992041661

A murine cDNA encodes a pan-epithelial glycoprotein that is also expressed on plasma cells

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Journal of Immunology ( J. IMMUNOL. ) (United States) 1992, 148/2  
(590-596)

CODEN: JOIMA ISSN: 0022-1767

DOCUMENT TYPE: Journal; Article

LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH



Using a subtractive cDNA approach, we have identified a number of genes expressed in murine plasmacytomas, but not B or pre-B lymphomas. One of these genes, 289A, expresses a 1.8-kb microsomally localized mRNA that encodes a 314-amino-acid protein containing a signal sequence and a hydrophobic transmembrane domain. Sequence comparison suggests that the predicted protein is the murine homologue of a human cell surface pan-epithelial glycoprotein known variously as EGP, GA733-2, KSA, and **KS1/4**, recognized by mAb HEA125, GA733, **KS1/4**, CO17-1A, M74, and 323/A3. The 289A mRNA is highly expressed in **normal** murine tissues containing epithelial cells, and at a low level in plasma cells induced by LPS stimulation of spleen B lymphocytes. It is expressed in 15 of 16 plasmacytomas, but at a much lower level, if at all, in pre-B or B lymphomas. In human B cell lines, 289A detects a 1.5-kb mRNA in the myeloma cell line 8226, but not in Burkitt's lymphoma or lymphoblastoid cell lines. Subsequent FACS analysis of human cell lines with the mAb GA733 and **KS1/4** demonstrated concordant expression of the mRNA and the protein. We conclude that 289A is the murine homologue of EGP, GA733-2, KSA, and **KS1/4** Ag. Although its expression was previously thought to be restricted to epithelial cells, it is also expressed in plasma cells and is a B lymphocyte differentiation Ag. Because of the multiplicity of names, we propose calling the human gene hEGP314, and the murine gene mEGP314.

8/7/10 (Item 4 from file: 73)  
 DIALOG(R) File 73:EMBASE  
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04629164 EMBASE No: 1991123207

Characterization of the colorectal carcinoma-associated antigen defined by monoclonal antibody D612

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 Cancer Research ( CANCER RES. ) (United States) 1991, 51/3 (926-934)  
 CODEN: CNREA ISSN: 0008-5472  
 DOCUMENT TYPE: Journal; Article  
 LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Monoclonal antibody (MAb) D612 recognizes an antigen expressed on the cell surface of **normal** and malignant gastrointestinal epithelium. It is a murine IgG2a/kappa which has been previously shown to mediate killing of human colon carcinoma cells using human effector cells (which could be enhanced in the presence of interleukin-2). Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) analyses of MAb D612 immunoprecipitates of extracts of L-(sup 3sup 5S)methionine-, L-(sup 3H)leucine-, and D-(sup 3H)glucosamine-labeled human colon carcinoma cells showed that the D612 antigen is a M(r) 48,000 glycoprotein. Similar estimates of molecular mass were obtained from SDS-PAGE analyses of MAb D612 immunoprecipitates of radioiodinated extracts of surgically resected colon carcinoma and adjacent **normal** colonic mucosa. D612 antigen was not detectable in immunoprecipitates of supernatant media from radiolabeled cell cultures, suggesting that the antigen is not readily shed from the surface of cultured cells. The D612 antigen was shown to be clearly distinct from previously described gastrointestinal carcinoma-associated glycoproteins: the D612 antigen shows a migration pattern of SDS-PAGE distinct from those of the antigens recognized by MAbs **KS1/4** and GA733, and reciprocal immunodepletion analyses of D-(sup 3H)glucosamine-labeled colon carcinoma cells utilizing MAbs D612 and GA733 revealed no cross-reactivity between these antibodies. Similarly, competitive binding studies between MAbs 17-1A and **KS1/4** and MAb D612 revealed no similarity between the epitopes recognized by MAb D612 and MAbs 17-1A and **KS1/4**. MAbs D612 and 17-1A were also titrated

in immunoperoxidase staining assays on serial frozen sections of **normal** and malignant colon. MAb D612 showed a higher titer of immunostaining reactivity with both **normal** and malignant colon than did MAb 17-1A. MAb D612 showed roughly equivalent immunostaining titers against **normal** and malignant colon; whereas MAb 17-1A showed a higher titer of immunostaining reactivity against the **normal** colon tissue than against the malignant colon. Flow cytometric analysis of phosphatidylinositol-specific phospholipase C-treated colon carcinoma cells revealed no loss of D612 antigen from the cell surface, suggesting that the mechanism of attachment of the D612 antigen to the cell surface does not involve linkage to a phosphatidylinositol glycan. Radioiodination of the D612 antigen in a plasma membrane-enriched cell fraction by the photoactivatable carbene-generating reagent, 3-(trifluoromethyl)-3-(m-(sup 1 sup 2sup 5I)iodophenyl)diazirine, suggests that the D612 antigen polypeptide penetrates the lipid bilayer of the plasma membrane. It has been determined by Scatchard analysis that the number of binding sites for MAb D612 on the LS-174T human colorectal carcinoma cell line is  $4.8 \times 10^5$ . MAb D612 was found to have a  $K(A)$  of approximately  $1.3 \times 10^9$  Msup -sup 1.

8/7/11 (Item 5 from file: 73)  
DIALOG(R) File 73:EMBASE  
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03555183 EMBASE No: 1988004619

Disposition of the monoclonal antibody-vinca alkaloid conjugate, **KS1/4-DAVLB** (LY256787), in Fischer 344 rats and rhesus monkeys  
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Drug Metabolism and Disposition ( DRUG METAB. DISPOS. ) (United States)  
1987, 15/5 (640-647)  
CODEN: DMDSA ISSN: 0090-9556  
DOCUMENT TYPE: Journal  
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

The conjugate, **KS1/4-DAVLB**, of the murine monoclonal antibody **KS1/4** with the vinca alkaloid 4-desacetylvinblastine (DAVLB) was administered intravenously to rats and monkeys. Terminal plasma half-life ( $t(1/2)$ ) values were measured as radioequivalents and as functionally immunoreactive antibody conjugate after dosing with **KS1/4-(sup 3H)DAVLB**. The  $t(1/2)$  values, determined radiometrically, were 145 hr and 62 hr in male rats after 10 and 100 mg/kg doses and 92 hr and 90 hr in male and female monkeys after a 40 mg/kg dose. Comparable results were obtained when the functionally immunoreactive conjugate concentrations were determined by an enzyme-linked immunosorbent assay technique. The ratio of sup 3sup 5S:sup 3H in the plasma after dosing rats with 100 mg/kg (sup 3sup 5S)**KS1/4-(sup 3H)DAVLB** remained reasonably constant during 336 hr. Less than 1% of the total vinca alkaloid equivalents present in the plasma at any time could be extracted as free vinca species; the major vinca alkaloid metabolites present at early time points were hemisuccinate derivatives of DAVALB, whereas, at later times, DAVALB and its N-oxide were equally as concentrated. The major pathway of elimination was fecal with about one-half of the administered radioactivity cleared in 150-250 hr. After dosing with (sup 3sup 5S)**KS1/4-(sup 3H)DAVLB**, the ratio of sup 3sup 5S:sup 3H radioactivity in the bile was substantially less than that in the plasma. Evaluation of radioactivity eluted from the bile by size-exclusion HPLC showed that almost all of the tritium was associated with material of lower molecular weight than that of **KS1/4-DAVLB**. These data suggest that the **KS1/4-DAVLB** conjugate circulated mostly in an intact form in the plasma and was catabolized in the liver with the subsequent excretion of vinca metabolites into the bile. The data are best described by a two-compartment

pharmacokinetic model which is consistent with the plasma kinetics and with the tissue distribution studies.

8/7/12 (Item 6 from file: 73)  
DIALOG(R) File 73:EMBASE  
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02740594 EMBASE No: 1984059553  
Antigens associated with a human lung adenocarcinoma defined by monoclonal antibodies  
Varki N.M.; Reisfeld R.A.; Walker L.E.  
Department of Immunology, Scripps Clinic and Research Foundation, La Jolla, CA 92037 United States  
Cancer Research ( CANCER RES. ) (United States) 1984, 44/2 (681-687)  
CODEN: CNREA  
DOCUMENT TYPE: Journal  
LANGUAGE: ENGLISH

Monoclonal antibodies KS1/4, KS1/9, and KS1/17 were developed in this laboratory from a fusion of the murine myeloma cell line P3X63Ag8 with spleens of BALB/c mice previously primed with UCLA P3 cells derived from a human adenocarcinoma of the lung. Monoclonal antibodies KS1/4 and KS1/17 seemed to recognize similar glycoprotein antigens on the lung carcinoma cells by indirect immunoprecipitation and sodium dodecyl sulfate-polyacrylamide gel electrophoresis analysis. However, mapping of (sup 3H)lysine- and (sup 3H)arginine-labeled tryptic peptides of antigens in specific immunoprecipitates of lung carcinoma cells by high-pressure liquid chromatography revealed a one peptide difference. Antibody KS1/9 did not immunoprecipitate any identifiable protein from detergent extracts of the immunizing cell line by routine methods and appears to detect a glycolipid antigen. Immunocytochemical analysis of tissue sections showed this monoclonal antibody to be reactive with adenocarcinomas of the lung and not with the other histological types of lung carcinoma or **normal** tissue. Monoclonal antibodies KS1/4 and KS1/17, however, reacted with 3 major histological types of lung **cancer** and minimally with the proximal tubules of **normal** kidney and the epithelium of bronchioles.

8/7/13 (Item 1 from file: 155)  
DIALOG(R) File 155:MEDLINE(R)

11096576 21101963 PMID: 11080501  
Determination of disulfide bond assignments and N-glycosylation sites of the human gastrointestinal carcinoma antigen GA733-2 (CO17-1A, EGP, KS1-4, KSA, and Ep-CAM).  
Chong J M; Speicher D W  
Wistar Institute, Philadelphia, Pennsylvania 19104, USA.  
Journal of biological chemistry (United States) Feb 23 2001, 276 (8) p5804-13, ISSN 0021-9258 Journal Code: 2985121R  
Contract/Grant No.: CA10815; CA; NCI; CA74294; CA; NCI  
Document type: Journal Article  
Languages: ENGLISH  
Main Citation Owner: NLM  
Record type: Completed  
The GA733-2 antigen is a cell surface glycoprotein highly expressed on most human gastrointestinal carcinoma and at a lower level on most **normal** epithelia. It is an unusual cell-cell adhesion protein that does not exhibit any obvious relationship to the four known classes of adhesion molecules. In this study, the disulfide-bonding pattern of the GA733-2 antigen was determined using matrix-assisted laser desorption/ionization mass spectrometry and N-terminal sequencing of purified tryptic peptides treated with 2-[2'-nitrophenylsulfonyl]-3-methyl-

3-bromoindolenine or partially reduced and alkylated. Numbering GA733-2 cysteines sequentially from the N terminus, the first three disulfide linkages are Cys1-Cys4, Cys2-Cys6, and Cys3-Cys5, which is a novel pattern for a cysteine-rich domain instead of the expected epidermal growth factor-like disulfide structure. The next three disulfide linkages are Cys7-Cys8, Cys9-Cys10, and Cys11-Cys12, consistent with the recently determined disulfide pattern of the thyroglobulin type 1A domain of insulin-like growth factor-binding proteins 1 and 6. Analysis of glycosylation sites showed that GA733-2 antigen contained N-linked carbohydrate but that no O-linked carbohydrate groups were detected. Of the three potential N-linked glycosylation sites, Asn175 was not glycosylated, whereas Asn88 was completely glycosylated, and Asn51 was partially glycosylated. These data show that the extracellular domain of the GA733-2 antigen consists of three distinct domains; a novel cysteine-rich N-terminal domain (GA733 type 1 motif), a cysteine-rich thyroglobulin type 1A domain (GA733 type 2 motif), and a unique nonglycosylated domain without cysteines (GA733 type 3 motif).

Record Date Created: 20010222

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Set	Items	Description
S1	7	(CO(W)17(W)1A) AND NORMAL
S2	3	RD S1 (unique items)
S3	11	(CO(W)17(W)1A) AND EXPRESSION
S4	5	RD S3 (unique items)
S5	168	KS1(W)4
S6	114	S5 AND (CANCER OR TUMOR OR TUMOUR)
S7	27	S6 AND NORMAL
S8	13	RD S7 (unique items)
?		